

PYRROLIZIDINE STUDIES: REDUCTIVE CYCLIZATION
OF NITROPARAFFIN ADDUCTS OF α -SUBSTITUTED
ACRYLIC ESTERS

BY

GRADUS LAWRENCE SHOEMAKER

A.B., Hope College, 1944

M.S., University of Illinois, 1947

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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INTRODUCTION

The reductive cyclization of γ -nitropimelates to pyrrolizidine or 8-alkylpyrrolizidines as developed by Leonard and coworkers^{1,2} offers the most convenient method for the preparation of these tertiary amines. The nitrocarboxylic esters that have been used were prepared by Bruson's method³ involving the addition of mononitroalkanes to esters of acrylic acid by a typical base-catalyzed Michael condensation. It was to be expected that the addition of nitroparaffins to α -substituted, α,β -unsaturated esters followed by reductive cyclization might give the 2,6-dialkyl- and the 2,6,8-trialkylpyrrolizidines. Also if the nitroparaffin adduct with one molecule of an α -substituted acrylic ester could be further condensed with a second molecule of an unsubstituted acrylic ester, reduction of the resulting nitroester would give the 2-alkyl- and the 2,8-dialkylpyrrolizidines. The object of this research was first, to seek conditions under which such Michael condensation might be effected, and second, to subject these nitroesters to the conditions for reductive cyclization.

An interesting study in the rearrangement of 1,2-chloroaminoalkanes was suggested by the synthesis of 8-hydroxymethylpyrrolizidine. After conversion to 8-chloromethylpyrrolizidine, it would possess a structure similar to the chloroamines which have rearranged.^{4,5} This rearrangement occurs through a cyclic ethylenimmonium ion, which can then undergo one of two types of nucleophilic substitution. Attack by a strongly nucleophilic ion such as hydroxyl proceeds by an S_N2 path with the attack taking place at the less substituted carbon. A second process (S_N1) would be a preliminary ring opening at the more alkylated carbon, giving a carbonium ion which would then react with the negative ion to yield a

rearranged product.

In the 8-chloromethylpyrrolizidine the formation of the cyclic intermediate would appear possible. However the opening of this ring to give a carbonium ion would not be likely, for the energy barrier to the formation of a planar configuration for this ion would be prohibitive. Therefore no rearrangement would be expected to occur if the postulated intermediates were correct. This part of the work was undertaken to test these theoretical considerations for an amine of the bicyclic type.

DISCUSSION OF RESULTS

The nitroesters of the type $RR'C(NO_2)CH_2-CH(CH_3)COOCH_3$ were prepared by the condensation of nitroparaffins with methyl methacrylate. A careful study of the conditions for this reaction indicated that the catalysts most effective for this Michael condensation were diethylamine and benzyltrimethylammonium hydroxide. Nitroparaffins used included nitromethane, nitroethane, 1-nitropropane and 2-nitropropane.

If R' was hydrogen, esters of the type $RC(NO_2)-[CH_2CH(CH_3)COOCH_3]_2$ could be prepared, preferably by the condensation of the mono-adduct with additional methyl methacrylate. The most effective catalyst for the synthesis of these substituted γ -nitropimelic esters was benzyltrimethylammonium butoxide. The synthesis of unsymmetrical γ -nitropimelic esters was likewise readily accomplished by the condensation of the mono-adduct with an additional molecule of an acrylic ester. Either the hydroxide or the butoxide of the quaternary ammonium salt was effective as the catalyst.

The condensation was also successfully extended to two other α,β -unsaturated esters, namely glutaconic and itaconic esters. Diethyl glutaconate condensed in good yield with nitromethane in the presence of benzyltrimethylammonium hydroxide. Both nitromethane and nitroethane condensed

with diethyl itaconate in the presence of diisopropylamine.

Bruson's condensation³ of nitroparaffins with acrylic esters has been extended to two new types of nitroparaffins. Ethyl nitroacetate reacted readily with ethyl acrylate to give both mono- and diconsensation products. Phenylnitromethane yielded a non-distillable oil when allowed to react with either the methyl or benzyl esters of acrylic acid.

The reductive cyclization of γ -nitropimelic esters to pyrrolizidines was extended to the syntheses of the 2-methyl-, the 2,6-dimethyl-, the 2,8-dimethyl-, the 2,6,8-trimethyl-, the 2-methyl-8-ethyl-, the 2,6-dimethyl-8-ethyl- and the 8-hydroxymethylpyrrolizidines. The reductive cyclization did not proceed satisfactorily with dimethyl γ -phenyl- γ -nitropimelate.

An attempt was made to extend the reductive cyclization method to the synthesis of the 1-*aza*-bicyclo[2,2,1]heptane series. However reduction of diethyl β -nitromethylglutarate and of ethyl β -carbethoxy- δ -nitrocaproate gave none of the desired bicyclic amines.

Treatment of 8-hydroxymethylpyrrolizidine with thionyl chloride yielded 8-chloromethylpyrrolizidine hydrochloride. Heating this salt above its melting point for one hour caused no rearrangement. Neither did liberation of the amine from its hydrochloride by means of alkali cause any change. The possibility of rearrangement during the preparation of 8-chloromethylpyrrolizidine was eliminated by the catalytic removal of the chlorine atom, yielding 8-methylpyrrolizidine, identified as its picrate and picrolonate. Thus conditions under which analogous 1-dialkylamino-2-chloroalkanes have rearranged caused no change in 8-chloromethylpyrrolizidine.

BIBLIOGRAPHY

1. Leonard, Hruda and Long, J. Am. Chem. Soc., 69, 690 (1947).

2. Leonard and Beck, *ibid.*, 70, 2504 (1948).
3. Bruson, U. S. Patent 2,342,119 (February 22, 1944) ; U. S. Patent 2,390,918 (December 11, 1945).
4. Kerwin, Ulliot, Fuson and Zirkle, J. Am. Chem. Soc., 69, 2961 (1947).
5. Fuson and Zirkle, *ibid.*, 70, 2760 (1948).

VITA

The author was born in Zeeland, Michigan, on January 18, 1921. He attended grammar school there, and was graduated from Zeeland High School in June, 1939. He entered Hope College in September, 1939, but illness forced him to withdraw during the year 1941-42. In September, 1942, he reentered, and received his Bachelor of Arts degree in June, 1944. After graduation he served in the U. S. Navy until December, 1945, when he was released to inactive duty. In March, 1946, he entered the Graduate School at the University of Illinois, and was granted the Master of Science degree in February, 1947. From March, 1946, to August, 1947, he was a part-time teaching assistant in organic chemistry. From September, 1947, to January, 1949, he held a University fellowship.



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